Exhibit 67

GYNECOLOGY

Association of genital talc and douche use in early adolescence or adulthood with uterine fibroids diagnoses

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BACKGROUND: Genital talc and douching are practices that can involve exposure to chemical compounds linked to certain gynecologic cancers. However, it is unclear if they are associated with fibroid risk or age at fibroid diagnosis among women.

OBJECTIVE: This study aimed to evaluate the impact of early-adolescence genital talc use and douching on prevalence of fibroids diagnosed before the age of 35 and 50 years among Black/African American and non-Hispanic White women.

STUDY DESIGN: Data were derived from the Sister Study (2003–2020), a prospective cohort of 50,884 US women aged 35 to 74 years at enrollment. Participants were asked if they ever had a fibroid diagnosis and at what age, and if they used genital talc and/or douched between the ages of 10 and 13 years or in the past 12 months. After applying predefined exclusion criteria, our analytical sample size was n=46,316 (Black, n=4310; non-Hispanic White, n=42,006). Multivariable logistic regression was used to compute adjusted odds ratios and 95% confidence intervals for having vs not having early-onset fibroids diagnosed before age 35 among women aged 35 to 74 years at enrollment, and fibroids diagnosed before age 50 among women aged 50 to 74 years at enrollment. We adjusted for early life factors (in utero diethylstilbestrol exposure, singleton or multiple birth, fed soy formula during infancy), childhood socioeconomic status, and relative weight and height compared with peers at age 10. We used multiple imputation (<10% missing in all analyses). Results were stratified by race/ethnicity given that Black women are more likely to develop fibroids at a younger age than non-Hispanic White women.

RESULTS: Among Black/African American women, 29% had fibroids diagnosed before age 35. Both genital talc use at age 10 to 13 (adjusted odds ratio, 1.23; confidence interval, 1.06–1.41) and douching (adjusted odds ratio, 1.19; 95% confidence interval, 0.95–1.48) were associated with higher odds of having a fibroid diagnosed before age 35. Douching without talc use was not associated with increased odds, but combined use of genital talc and douche was associated with 52% increased odds of fibroids (confidence interval, 1.14–2.01). Among non-Hispanic White women, 9% reported fibroids diagnosed before age 35. Genital talc use (1.31; 1.20–1.44) but not douching (0.96; 0.77–1.20) at age of 10 to 13 years was associated with having a fibroid diagnosed before age 35. We observed similar patterns for non-Hispanic White women when we considered fibroids diagnosed before age 50, but neither practice was associated with fibroids diagnosed before age 50 in Black women.

CONCLUSION: Genital talc use in early adolescence, alone and in combination with douching (but not douching alone), is associated with prevalence of fibroids diagnosed before age 35 among Black/African American women and before ages 35 and 50 among non-Hispanic White women. Early adolescence may be a window of susceptibility for fibroid development, suggesting that adolescent girls should be educated on abstention from or alternatives to talc use and douching.

Key words: adolescence, douching, feminine hygiene, fibroids, genital talc, leiomyoma, women

Introduction

Uterine leiomyomas, known as fibroids, are hormone-dependent benign tumors of the uterine muscle.[1] They are the most common indication for hysterectomy in the United States.[2–4] Fibroids can result in high morbidity including heavy bleeding, anemia,[5] depression, and anxiety that may adversely affect quality of life.[6] Symptomatic fibroids can be treated with medications, interventional radiology, or surgery.[1,7] In 2012, the estimated annual cost of uterine fibroids in the United States was $5.9 to $34.4 billion.[8] Black women have a higher prevalence of early-onset fibroids (age ≤30 years) than White women,[4,9,10] and are more likely to develop larger or more symptomatic fibroids[11] that require invasive treatment, including hysterectomy.[4,11]

Genital talc use and douching are intimate care practices with adverse gynecologic health effects.[12–15] Previous studies have found associations between genital talc use and fibroids,[16] and uterine cancer,[17] and douching has been associated with cervical cancer.[18] Talc is a poorly soluble particle, and animal models have shown that once deposited onto epithelial cells, it can cause chronic inflammation, leading to a series of mutagenic events, and this effect is worse in talc contaminated with asbestos, a known carcinogen.[19] Some douching products contain phthalates,[20,21] which are endocrine-disrupting chemicals (EDCs) that can be detrimental to human health.[22] Use of intimate care products is strongly influenced by targeted marketing of products,[23] cultural beliefs, and educational factors.[24] Black women are more likely to use genital talc

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AJOG at a Glance

Why was this study conducted?

The adolescent period may be a window of susceptibility to fibroid development. Exposure to known/suspected carcinogens during this period may influence fibroid risk. This study investigated whether genital talc use and douching in early adolescence affect fibroid risk.

Key findings

Among Black/African American women, genital talc use at age of 10 to 13 years was associated with 23% increased odds of fibroid diagnosis before age 35. Although douching alone was not associated with fibroid risk, the combined use of genital talc and douching at ages 10 to 13 was associated with 52% increased odds of fibroid diagnosis. Among non-Hispanic White women, genital talc use at age 10 to 13 was associated with 31% higher odds of fibroids, but risk was similar when we considered combined douching and talc use. Results were similar for fibroids diagnosed up to the age of 50 years.

What does this add to what is known?

Genital talc use is associated with increased fibroid prevalence. This information may guide interventions regarding intimate care practices.

and douching than women from other cultures.[23,25] Age of first douche is found to be correlated positively with age of menarche,[24,26] early menarche is associated with an increased risk of fibroids,[27] and Black girls are more likely to begin puberty early.[28]

In this study, we were interested in exploring whether early use of genital talc or douching may affect the risk of fibroids and age at fibroid onset. Given the potential for talc and douching to alter the female genital tract, we hypothesized that exposure to genital talc and douching in early adolescence would increase the risk of fibroids diagnosed at a younger age, and that exposure in early adolescence and in adulthood would be associated with higher rates of subsequent fibroid incidence.

Materials and Methods

Study population

The Sister Study is a prospective cohort of 50,844 women (enrolled from 2003–2009, aged 35–74 years) exploring environmental and genetic risk factors for breast cancer and other diseases.[29] Participants had at least 1 sister with a history of breast cancer but had never had breast cancer themselves. All participants completed a computer-assisted telephone interview and an in-home evaluation.

Exposure and outcome assessment

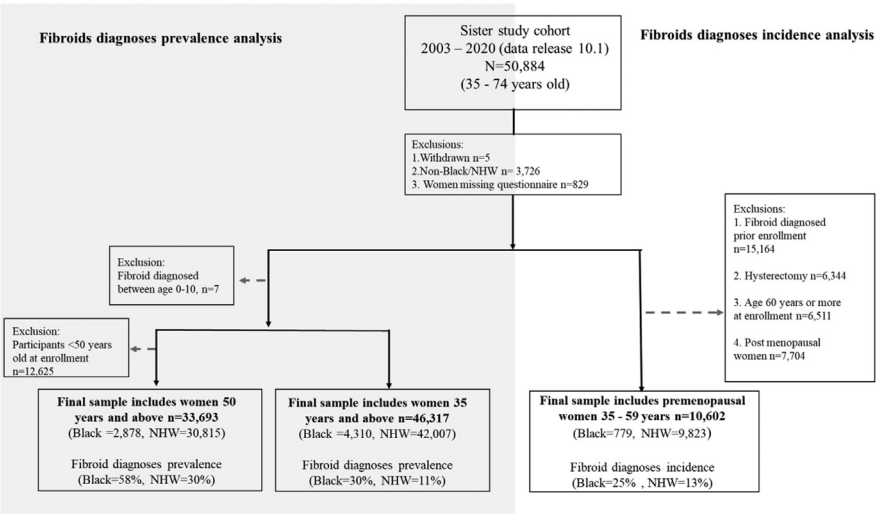
Participants were asked if they used genital talc or douched between the ages of 10 and 13 years (early adolescence), and in the 12 months before enrollment (as a marker for recent use). Genital talc use was defined as the application of "talcum powder to a sanitary napkin, underwear, diaphragm, cervical cap, or directly to your vaginal area." For use between 10 and 13 years, and 12 months before enrollment, participants provided information on whether they did not use, sometimes used, or frequently used genital talc or douche.[30] Further, we created variables for combined use of both genital talc and douching, "douching/no talc," "talc/no douching," or neither during the relevant time periods. Participants were asked at enrollment and during follow-up if they had ever been diagnosed with fibroids by a doctor or a health professional and at what age. We analyzed the association of exposures with self-reported clinically diagnosed fibroids either by age 35 or by age 50 (hereafter referred to as fibroid prevalence) and fibroids diagnosed after study enrollment (fibroid incidence). For all analyses, we excluded women who withdrew from the study (n=5), reported a fibroid diagnosis before age 11 (n=7), or did not answer the personal care product use questionnaire (n=829). Because of the small sample size, we excluded women who identified as a race and ethnicity other than Black/African American (referred to as Black) or non-Hispanic White (NHW) (n=3726) (Figure).

For all analyses, we conducted multiple imputation for missing values. Our primary focus was imputing values for frequency of talc use (3% from incidence and 4% from prevalence analysis), douching (0% and 1%), and fibroid diagnosis age (0% and 10%). We assumed that these were missing at random depending on the specified covariates, and obtained 10 imputation data sets using SAS PROC MI (SAS Institute, Cary, NC).[31] The multiple-imputation regression models included fibroid status, age at baseline, body mass index (BMI) at baseline, hysterectomy, socioeconomic status (SES), talc and douching frequency, parity, age at last birth, age at first birth, early life exposure factors (multiple birth, diethylstilbestrol [DES] use), relative height and weight compared with peers at age 10, duration of hormonal birth control, pelvic inflammatory disease, genital herpes, and chlamydia diagnosis. We additionally conducted a complete-case analysis to assess our primary results for bias. Wald statistics were used to calculate trend tests for frequency of product use. Given the higher rates and earlier onset of fibroids among Black women and potential for differential risk factors, we stratified our analysis by race, examining associations separately for Black and NHW participants. SAS software, version 9.4 (SAS Institute) was used. The Sister Study was approved by the Institutional Review Board of the National Institutes of Health (IRB00001313). Written informed consent was obtained from all participants.

Prevalence analysis

We evaluated whether exposure to talc or douching during adolescence (independently or in combination) is associated with fibroid prevalence. First, we compared those with fibroids diagnosed before age 35 with those not diagnosed before 35 (4310 Black and 42,006 NHW). We explored the relative excess

FIGURE
Flowchart of study participants for fibroid prevalence and incidence analysis



NHW, non-Hispanic White.

Ogunsina. Association of genital talc use and douching with fibroids. Am J Obstet Gynecol 2023.

risk (RERI) for the interaction of talc use and douching on fibroids, comparing everyone with the common referent group of no talc or douche use.[32,33]

Secondly, we compared those diagnosed before age 50 with those not diagnosed before 50, limiting the sample to those aged 50 to 74 years at enrollment (2878 Black and 30,815 NHW) (Figure).

We used multivariable logistic regression models to estimate the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association of adolescent genital talc and douching with fibroids diagnosed before enrollment. Regression models were combined using SAS PROC MIANALYZE. All models were adjusted for potential confounders identified from Table 1 and from previous publications as possibly being associated with fibroids and use of talc or douche: age at enrollment, highest education level in household at age 13, and childhood SES defined using self-report of family's income level during most of the time growing up (well-off, middle income, low income, or poor). In addition, we adjusted for relative height (shorter, same, taller) and weight (thinner, same, heavier) compared with peers at age 10, and early life factors previously found to be associated with fibroid development in the Sister Study[34]: fed soy formula as an infant, born as a singleton or member of multiple births, and in utero exposure to DES. We did not adjust for menarche in the main analysis because not everyone in the analytical sample had menarche at the time of exposure (10−13 years), but we conducted a sensitivity analysis restricting the data to participants who experienced menarche at age of ≤13 years.

Incidence analysis

We excluded participants aged >60 years at enrollment (n=7704) and those with preenrollment fibroid diagnoses (n=15,164), hysterectomy (n=6344), or menopause (n=7704), resulting in 779 Black and 9822 NHW participants (Figure). The exposures of interest were talc and douching at age 10 to 13 and at 12 months before enrollment. Covariates of interest for use in the model for exposure at age 10 to 13 were the same as those used in the prevalence analysis. For the association of exposures 12 months before enrollment with incident fibroids, we additionally considered covariates potentially associated with fibroids and adulthood use of genital talc or douching, including duration of hormonal birth control use, age at last childbirth, parity, BMI at enrollment, age at menarche, highest educational level attained as an adult, adult SES (total household income 12 months before enrollment), alcohol use, cigarette use, and talc use, or douching at age 10 to 13 (depending on the exposure modeled). We used multivariable Cox proportional hazards models to estimate hazard ratios (HRs) and 95% CIs, with age as the time scale, following participants from enrollment to age at fibroid diagnosis, censoring at age of hysterectomy, menopause, 60 years, loss to follow-up, end of follow-up (October 2020; data release 10.1), or death, whichever came first.

Results

Sociodemographic characteristics of women aged 35 to 74 years are shown in Table 1. Among Black participants, the mean age at enrollment for both those with and without fibroids was 54, and those who reported fibroids were more likely to have postgraduate education in adulthood (30%) than those who did not (25%). They were also less likely (21%) to have ≥3 children than those who did not have fibroids (28%). Among NHW participants, mean age at enrollment for those without fibroids was 56 and for those with fibroids 57 years. Those who reported fibroids were more likely (23%) to have been aged ≤25 years at last childbirth compared with those without fibroids (16%).

Fibroid prevalence and adolescent (age of 10−13 years) exposures

Black women

Fibroids before the age of 35 years.

Among 4310 Black women, 29% reported a fibroids diagnosis before the age of 35 years. Genital talc use was associated with increased odds of fibroids diagnosed before age 35 (aOR, 1.23; 95% CI, 1.06−1.41). The aORs were similar for occasional and frequent users. Compared with those who never douched, those who douched had increased odds of developing fibroids (1.19; 0.95−1.48); however, most (59%) of those who

TABLE 1
Baseline characteristics of Black and non-Hispanic White Sister Study participants aged 35 to 74 years in the prevalence analysis, stratified by fibroid status at age 35

Characteristics (N=46,316 [100%])	Black women (n=4310)		NHW women (n=42,006)	
	No fibroid diagnosed before age 35	Fibroid diagnosed before age 35	No fibroid diagnosed before age 35	Fibroid diagnosed before age 35
	n=3058 (71)	n=1252 (29)	n=38,142 (91)	n=3864 (9)
Childhood factors				
Menarche age in y (SD)	12.6 (2)	12.3 (2)	12.7 (2)	12.5 (2)
Height relative to peers (age 10 y)				
Shorter	900 (29)	364 (29)	9343 (24)	970 (25)
Same	1427 (46)	553 (44)	17,604 (46)	1755 (45)
Taller	731 (24)	335 (27)	11,196 (29)	1139 (29)
Weight relative to peers (age 10 y)				
Thinner	1242 (41)	564 (45)	12,868 (34)	1332 (34)
Same	1332 (44)	511 (41)	18,116 (48)	1783 (46)
Heavier	484 (16)	177 (14)	7158 (19)	749 (19)
Highest education in childhood household[a]	n (%)	n (%)	n (%)	n (%)
High school or less	2240 (73)	907 (72)	19,449 (51)	2105 (54)
Some college	482 (16)	200 (16)	7486 (20)	963 (20)
College degree	223 (7)	101 (8)	6820 (18)	596 (15)
Postgraduate degree	113 (4)	44 (4)	4387 (12)	399 (10)
Childhood SES[b]				
Poor	566 (19)	245 (20)	2148 (6)	313 (8)
Low	1119 (37)	471 (38)	9289 (24)	974 (25)
Middle	1288 (42)	498 (40)	24,075 (63)	2336 (61)
Well-off	85 (3)	38 (3)	2631 (7)	240 (6)
Maternal pregnancy and early life factors				
DES use				
Definitely/probably	45 (1)	27 (2)	1036 (3)	152 (4)
Definitely not/probably not	3013 (99)	1225 (98)	37,106 (97)	3712 (96)
Multiple births				
Single birth	2961 (97)	1196 (96)	36,929 (97)	3743 (97)
Multiple birth	97 (3)	56 (4)	1214 (3)	121 (3)
Fed soy formula				
Definitely/probably	95 (3)	42 (3)	1043 (3)	138 (3)
Definitely not/probably not	2963 (97)	1210 (97)	37,099 (97)	3726 (97)
Adult factors				
Body mass index in kg/m^2 at baseline (SD)	31.3 (7)	31.3 (6)	27.3 (6)	28.1 (6)
Mean age at baseline in y (SD)	53.6 (8)	54.1 (8)	56.0 (9)	57.0 (9)
Adult SES[c]				
Poor	219 (7)	70 (6)	1337 (4)	150 (4)

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TABLE 1
Baseline characteristics of Black and non-Hispanic White Sister Study participants aged 35 to 74 years in the prevalence analysis, stratified by fibroid status at age 35 *(continued)*

Characteristics (N=46,316 [100%])	Black women (n=4310)		NHW women (n=42,006)	
	No fibroid diagnosed before age 35	Fibroid diagnosed before age 35	No fibroid diagnosed before age 35	Fibroid diagnosed before age 35
	n=3058 (71)	n=1252 (29)	n=38,142 (91)	n=3864 (9)
Low	816 (27)	315 (25)	7632 (20)	824 (21)
Middle	1266 (41)	544 (43)	15,718 (41)	1636 (42)
Well-off	758 (25)	323 (26)	13,455 (35)	1254 (32)
Adult educational level[d]				
High school or less	363 (12)	96 (8)	5815 (15)	626 (16)
Some college	1109 (36)	434 (35)	12,596 (33)	1438 (37)
College degree	809 (26)	350 (28)	10,487 (28)	891 (23)
Postgraduate degree	777 (25)	371 (30)	9244 (24)	909 (24)
Duration of hormonal birth control use				
None	414 (14)	159 (13)	5940 (16)	598 (15)
<2 y	436 (14)	166 (13)	6097 (16)	761 (20)
2–10 y	1266 (41)	558 (45)	16,698 (44)	1708 (44)
>10 y	942 (31)	369 (29)	9407 (25)	797 (21)
Age at last childbirth				
No birth	296 (10)	171 (14)	4921 (13)	497 (13)
<25 y	818 (27)	375 (30)	6073 (16)	879 (23)
25–34 y	1518 (50)	568 (45)	21,145 (55)	2005 (53)
≥35 y	426 (14)	139 (11)	6003 (16)	483 (12)
Parity				
Nullipara	510 (17)	280 (22)	6971 (18)	702 (18)
1	651 (21)	324 (26)	5091 (13)	629 (16)
2	1046 (34)	386 (31)	14,233 (37)	1412 (37)
≥3	851 (28)	262 (21)	11,847 (31)	1120 (29)
Alcohol use				
Never	174 (6)	70 (6)	1159 (3)	136 (4)
Past	764 (25)	297 (24)	5202 (14)	601(16)
Current nonregular drinker	487 (16)	188 (15)	2624 (7)	301 (8)
Current regular drinker	1634 (53)	697 (56)	29,158 (76)	2826 (73)
Cigarette use				
Never	1950 (64)	777 (62)	20,873 (55)	2076 (54)
Past smoker	814 (27)	341 (27)	14,297 (37)	1426 (37)
Current smoker	294 (10)	135 (11)	2972 (8)	362(9)

Percentages may not add up to 100 because of rounding up. Imputed numbers may not add up exactly to total n's because of rounding.

DES, diethylstilbestrol; *NHW*, non-Hispanic White; *SES*, socioeconomic status.

[a] Highest education level in household at age of 13 years; [b] Childhood SES is defined as family's income level during most of the time growing up; [c] Adult SES is defined as total income from all household members last year before taxes; [d] Highest educational level attained as an adult.

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TABLE 2
Association of fibroid diagnoses before the age of 35 years with talc and douching in early adolescence (age 10–13) among Black and non-Hispanic White women in the Sister Study

	Black women (n=4310)			NHW women (n=42,006)		
Genital talc use and douching characteristics	No fibroid before age 35, n (%)=3058 (71)	Fibroid diagnosed before age 35, n (%)=1252 (29)	Adjusted OR (95% CI)	No fibroid before age 35, n (%)= 38,142 (91)	Fibroid diagnosed before age 35, n (%)=3864 (9)	Adjusted OR (95% CI)
Talc use at age of 10–13 y[a]						
No	2003 (66)	761 (61)	Ref	31,422 (82)	3008 (78)	ref
Yes	1055 (35)	491 (39)	1.23 (1.06–1.41)	6720 (18)	856 (22)	1.31 (1.20–1.44)
Frequency of talc use[b]						
Nonusers	2003 (66)	761 (61)	Ref	31,422 (82)	3008 (78)	Ref
Sometimes	815 (27)	380 (30)	1.23 (1.05–1.44)	5819 (15)	728 (19)	1.29 (1.17–1.42)
Frequently	241 (8)	111 (9)	1.21 (0.93–1.57)	902(2)	128 (3)	1.44 (1.15–1.80)
P for trend			.01			<.01
Douching at age of 10–13 y[c]						
No	2773 (91)	1118 (89)	Ref	37,158 (97)	3771 (98)	Ref
Yes	286 (9)	134 (11)	1.19 (0.95–1.48)	985 (3)	93 (2)	0.96 (0.77–1.20)
Combined use at age of 10–13 y						
Nonusers[d]	1875 (61)	717 (57)	Ref	30,862 (81)	2962 (77)	Ref
Talc/no douching[e]	898 (29)	400 (32)	1.17 (1.00–1.36)	6296 (16)	809 (21)	1.32 (1.20–1.45)
Douching/no talc[f]	128 (4)	44 (4)	0.93 (0.64–1.34)	560 (1)	46 (1)	0.89 (0.66–1.22)
Both[g]	157 (5)	90 (7)	1.52 (1.14–2.01)	424 (1)	47 (1)	1.16 (0.84–1.61)

Model adjusted for age at baseline, highest educational level in household at age 13, childhood socioeconomic status, weight and height relative to peers at age 10, maternal diethylstilbestrol use, fed soy formula, and product of multiple birth. Percentages may not add up to 100 because of rounding up. Imputed numbers may not add up because of rounding. Frequency of douching is not reported because of small sample size (n<10) and for participant confidentiality purposes.

CI, confidence interval; *NHW*, non-Hispanic White; *OR*, odds ratio.

[a] Any talc use (includes occasional and frequent users); [b] Frequency of use in early adolescence (never, sometimes, frequently); [c] Any douche use; [d] Used neither genital talc nor douche; [e] Used talc but not douche; [f] Used douche but not talc; [g] Used both genital talc and douche.

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douched also used talc. Douching without talc use was not associated with fibroids (0.93; 0.64–1.34). Compared with no use of either product, combined use of talc and douching was also associated with fibroids (1.52; 1.14–2.01) (Table 2). The joint effect was positive, although the CI included the null (RERI=0.41; 95% CI: -0.14 to 1.35).

Fibroids before the age of 50 years.

Among 2878 Black women aged >50 years at enrollment, 58% reported a fibroid diagnosed before age 50. The aOR for the association between genital talc use and fibroids was 1.10 (0.94–1.29), with no evidence of a dose–response relationship. Douching was not associated with fibroids diagnosed by age 50 (1.05; 0.81–1.38), although combined use of talc and douching had an elevated aOR (1.19; 0.87–1.65) (Table 3).

Non-Hispanic White women

Fibroids before the age of 35 years.

Among 42,006 NHW women, the prevalence of fibroids before the age of 35 years was 9%. Genital talc use was associated with fibroids before age 35 (1.31; 1.20–1.44) with a positive trend for frequency of use (*P* for trend <.01; aOR, 1.44; 1.15–1.80 for frequent users). Douching in childhood was uncommon (2%–3%) and was not independently associated with fibroids (0.96; 0.77–1.20). Compared with no use, the aOR for fibroids associated with combined use was 1.16 (0.84–1.61) (Table 2), with little evidence of an interaction (RERI=–0.07; 95% CI, –0.54 to 0.41).

Fibroids before the age of 50 years.

Among 30,816 NHW women, 30% reported fibroids before the age of 50 years. Fibroid prevalence was associated with genital talc use (1.26; 1.18–1.34) with a slightly positive trend for frequency of use (*P* for trend <.01; aOR, 1.29; 1.11–1.49 for frequent users). Douching was not associated with fibroids (1.01; 0.85–1.19). Compared with no use, the aOR for fibroids associated with combined use of talc and douche was 1.40 (1.11–1.77) (Table 3).

TABLE 3
Association of fibroid diagnoses before the age of 50 years with talc and douching in early adolescence (age 10–13) among Black and non-Hispanic White women in the Sister Study

	Black women (n=2878)			NHW women (n=30,816)		
Genital talc use and douching characteristics	No fibroid before age 50, n (%)= 1213 (42)	Fibroid diagnosed before age 50, n (%)=1665 (58)	Adjusted OR (95% CI)	No fibroid before age 50, n (%)= 21,625 (70)	Fibroid diagnosed before age 50, n (%)= 9191 (30)	Adjusted OR (95% CI)
Talc use at age of 10–13 y[a]						
No	767 (63)	1020 (61)	Ref	17,751 (82)	7201 (78)	Ref
Yes	446 (37)	645 (39)	1.10 (0.94–1.29)	3874 (18)	1990 (22)	1.26 (1.18–1.34)
Frequency of talc use[b]						
Nonuser	767 (63)	1020 (61)	Ref	17,751 (82)	7201 (78)	Ref
Sometimes	341 (28)	489 (29)	1.10 (0.92–1.30)	3318 (15)	1698 (18)	1.26 (1.18–1.34)
Frequently	106 (9)	156 (9)	1.11 (0.84–1.46)	556 (3)	292 (3)	1.29 (1.11–1.49)
P for trend			.28			<.01
Douching at age of 10–13 y[c]						
No	1100 (91)	1501 (90)	Ref	21,152 (98)	8989 (98)	Ref
Yes	113 (9)	164 (10)	1.05 (0.81–1.38)	473 (2)	202 (2)	1.01 (0.85–1.19)
Combined use at age of 10–13 y						
Nonusers[d]	725 (60)	970 (58)	Ref	17,480 (81)	7114 (77)	Ref
Talc/no douching[e]	375 (31)	531 (32)	1.07 (0.90–1.27)	3672 (17)	1875 (20)	1.25 (1.17–1.33)
Douching/no talc[f]	42 (3)	50 (3)	0.89 (0.56–1.40)	271 (1)	87 (1)	0.80 (0.62–1.02)
Both[g]	71 (6)	114 (7)	1.19 (0.87–1.65)	202 (1)	115 (1)	1.40 (1.11–1.77)

Model adjusted for age at baseline, highest educational level in household at age 13, childhood socioeconomic status, weight and height relative to peers at age 10, maternal diethylstilbestrol use, fed soy formula, and product of multiple birth. Percentages may exceed 100 because of rounding up. Imputed numbers may not add up to total n's because of rounding. Frequency of douching is not reported because of small sample size (n<10) and for participant confidentiality purposes.

CI, confidence interval; *NHW*, non-Hispanic White; *OR*, odds ratio.

[a] Any talc use (includes occasional and frequent users); [b] Frequency of use in early adolescence (never, sometimes, frequently); [c] Any douche use; [d] Used neither genital talc nor douche; [e] Used talc but not douche; [f] Used douche but not talc; [g] Used both genital talc and douche.

Ogunsina. Association of genital talc use and douching with fibroids. Am J Obstet Gynecol 2023.

Sensitivity analysis

Results were largely unchanged in sensitivity analyses examining fibroids before age 35 among participants who reached menarche at ≤13 years (Supplemental Table 1).

Analysis of fibroid incidence

With follow-up of up to 16 years (average, 6), 195 Black women and 1424 NHW women developed fibroids. There was little evidence for an association of talc or douching with incidence of fibroids among premenopausal Black women with adolescent or adult exposure. Among premenopausal NHW women, genital talc use was also not associated with fibroids. However, douching in early adolescence was associated with increased fibroid incidence, with an adjusted HR of fibroids of 1.48 (1.15–1.92) (Supplemental Table 2).

Comment

Principal findings

The use of genital talc in early adolescence was associated with increased odds of fibroids diagnosed before the age of 35 years among both Black and NHW women, and fibroids diagnosed before age 50 among NHW women. Douching in early adolescence was not associated with prevalence of fibroids in the absence of genital talc, and findings regarding associations with combined use of talc and douching were similar to those regarding the use of genital talc overall. However, among Black participants using both products, there were higher odds of fibroids before age 35 compared with never-users, and the combined effect of talc and douche was potentially greater than the sum of their individual effects. Among NHW participants, the combined effect was negligible.

Results in the context of what is known

Genital talc use and douching are widely used intimate care practices despite evidence that they may be detrimental to reproductive health.[12,15,35,36] Like others, we found a high prevalence of fibroids,[4,37] genital talc use, and douching among Black women.[23,25,38] Our finding that early adolescent genital talc use was associated with increased odds of fibroids diagnosed before the age of 35 years was similar to the results of a cross-sectional study by Wright et al,[16] who found a positive association between perineal talc use and increased fibroid prevalence among Black women aged 23 to 35 years. A clinic-based case−control study in Baltimore found that the aOR for fibroids with perineal talc use increased with frequency of use.[39]

We did not observe clear associations between douching in early adolescence and prevalence of fibroids, which was again consistent with previous findings among Black women aged <35 years.[16] We did observe a modestly elevated risk for fibroids diagnosed before age 35 among Black women using douching and talc. We speculate that the process of douching may help the ascension of talc particles further up into the reproductive tract, depositing more talc particles in the uterus. However, more research is needed in this area. We found increased incidence of fibroids diagnosed after enrollment among NHW women with a history of douching in early adolescence but not in the 12 months before study enrollment, which could suggest a longer latency period for douching.

Clinical implications

There is no medical indication for genital talc or douching for hygienic purposes. In the early 1970s, talc used in cosmetics was found to be contaminated with asbestos, a known carcinogen,[40] and in 1976, industry-sponsored specifications were made for asbestos-free cosmetic talc products.[41] The mean age of study participants at enrollment was 54 years for Black and 57 years for NHW women, indicating their risk of exposure to earlier talc products. Talc is considered by the International Agency for Research on Cancer as possibly carcinogenic.[19] Furthermore, talc is hypothesized to negatively affect the female reproductive tract,[42−44] and has been shown to cause inflammation in ovarian cells in animal studies, contributing to neoplastic transformation and tumor growth.[45] We hypothesize that regular use of talc-based products could result in chronic myometrial inflammation, which can damage cellular proteins and DNA.[46−48] Fibroids are dependent on progesterone and estrogen for growth,[49] and during adolescence there are rapidly increasing estrogen and progesterone levels.[50,51] Fibroid onset may correlate with active or chronic inflammation,[52] and inflammation coupled with high estrogen and progesterone levels could create a microenvironment conducive to fibrinogenesis.[53]

Although this research cannot establish a causal relationship between genital talc use, douching, and the occurrence of fibroids, the accumulating evidence that these intimate care practices may have negative health effects could provide clinicians with further information for discouraging their use. Both adolescents and adults should be informed about potential risks of talc and douching so that they can make informed decision regarding use.

Research implications

A large prospective study of young women (aged <35 years) with regular ultrasound monitoring and detailed life-course data on the exposures could provide clarity on this important research question. Talc use and douching should be further explored, including consideration of types of products used, patterns, frequency, and duration of use. Laboratory studies may help us explore the effects of estrogen, talc, and EDCs on uterine cell growth and fibroid development.

Strengths and limitations

The study participants were US women who had a sister diagnosed with breast cancer, which may limit generalizability. Our use of self-reported data is subject to recall or reporting bias; however, a previous study found good consistency in recall of use of intimate care products among women in the Sister Study.[30] There is potential for misclassification of fibroids given that some women may be undiagnosed,[54] and transvaginal ultrasound scans were not feasible for the large Sister Study cohort. Therefore, we are unable to rule out the presence of undiagnosed fibroids at enrollment and during follow-up. Data on family history of fibroids are not available, and we were unable to adjust for family history. Measurement of exposure at 12 months before enrollment may not adequately reflect use in adulthood given that use of both products decreases with age and is less common after menopause.[30] Because the use of such products may be related to menstruation, we censored incident analysis at time of menopause, which can limit the misclassification. Given the age at study enrollment and the early onset of fibroids in Black women, a smaller number of Black women were eligible for the analysis of fibroid incidence, resulting in an underestimation of overall fibroid risk. In view of these limitations and challenges, our incidence analysis findings can be considered preliminary. However, our approach may help inform the design and implementation of future prospective studies. Key strengths of this study include the large sample size of women and the life course approach to examining genital talc and douching.

Conclusions

This study suggests that early-adolescent genital talc use is associated with increased odds of uterine fibroids diagnosed before the age of 35 years among Black women and before age 35 and 50 among NHW women. Douching in early adolescence is positively associated with fibroid prevalence, but not when considered independently of talc. Preliminary findings suggest that douching may be positively associated with incidence of fibroids. For both types of intimate care practices, adolescence may serve as a window of susceptibility during which the effects of exposure combine with increasing estrogen levels, adversely affecting uterine tissue and stimulating fibroid growth. The

associations observed herein, combined with similar findings from other observational studies, suggest that health practitioners should ask women and adolescents about their intimate care product use and provide counsel about their possible adverse health effects. ■

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References

1. Giuliani E, As-Sanie S, Marsh EE. Epidemiology and management of uterine fibroids. Int J Gynaecol Obstet 2020;149:3–9.
2. Merrill RM. Hysterectomy surveillance in the united states, 1997 through 2005. Med Sci Monit 2008;14:CR24–31.
3. Laughlin SK, Schroeder JC, Baird DD. New directions in the epidemiology of uterine fibroids. Semin Reprod Med 2010;28:204–17.
4. Baird DD, Dunson DB, Hill MC, Cousins D, Schectman JM. High cumulative incidence of uterine leiomyoma in black and white women: ultrasound evidence. Am J Obstet Gynecol 2003;188:100–7.
5. Levens ED, Wesley R, Premkumar A, Blocker W, Nieman LK. Magnetic resonance imaging and transvaginal ultrasound for determining fibroid burden: implications for research and clinical care. Am J Obstet Gynecol 2009;200:537.e1–7.
6. Ghant MS, Sengoba KS, Recht H, Cameron KA, Lawson AK, Marsh EE. Beyond the physical: A qualitative assessment of the burden of symptomatic uterine fibroids on women's emotional and psychosocial health. J Psychosom Res 2015;78:499–503.
7. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Alternatives to hysterectomy in the management of leiomyomas. Obstet Gynecol 2008;112:387–400.
8. Cardozo ER, Clark AD, Banks NK, Henne MB, Stegmann BJ, Segars JH. The estimated annual cost of uterine leiomyomata in the united states. Am J Obstet Gynecol 2012;206:211.e1–9.
9. Marshall LM, Spiegelman D, Barbieri RL, et al. Variation in the incidence of uterine leiomyoma among premenopausal women by age and race. Obstet Gynecol 1997;90:967–73.
10. Marsh EE, Ekpo GE, Cardozo ER, Brocks M, Dune T, Cohen LS. Racial differences in fibroid prevalence and ultrasound findings in asymptomatic young women (18-30 years old): a pilot study. Fertil Steril 2013;99:1951–7.
11. Kjerulff KH, Langenberg P, Seidman JD, Stolley PD, Guzinski GM. Uterine leiomyomas. Racial differences in severity, symptoms and age at diagnosis. J Reprod Med 1996;41:483–90.
12. Jenkins A, Money D, O'Doherty KC. Is the vaginal cleansing product industry causing harm to women? Expert Rev Anti Infect Ther 2021;19:267–9.
13. Fashemi B, Delaney ML, Onderdonk AB, Fichorova RN. Effects of feminine hygiene products on the vaginal mucosal biome. Microb Ecol Health Dis 2013;24:19703.
14. Gabriel IM, Vitonis AF, Welch WR, Titus L, Cramer DW. Douching, talc use, and risk for ovarian cancer and conditions related to genital tract inflammation. Cancer Epidemiol Biomarkers Prev 2019;28:1835–44.
15. Cottrell BH. An updated review of of evidence to discourage douching. MCN Am J Matern Child Nurs 2010;35:102–7.
16. Wright MA, Moore KR, Upson K, Baird DD, Chin HB. Douching or perineal talc use and prevalent fibroids in young African American women. J Womens Health (Larchmt) 2021;30:1729–35.
17. O'Brien KM, D'Aloisio AA, Shi M, Murphy JD, Sandler DP, Weinberg CR. Perineal talc use, douching, and the risk of uterine cancer. Epidemiology 2019;30:845–52.
18. O'Brien KM, Weinberg CR, D'Aloisio AA, Moore KR, Sandler DP. The association between douching, genital talc use, and the risk of prevalent and incident cervical cancer. Sci Rep 2021;11:14836.
19. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Carbon black, titanium dioxide, and talc. IARC Monogr Eval Carcinog Risks Hum 2010;93:1–413.
20. Branch F, Woodruff TJ, Mitro SD, Zota AR. Vaginal douching and racial/ethnic disparities in phthalates exposures among reproductive-aged women: National Health and Nutrition Examination Survey 2001-2004. Environ Health 2015;14:57.
21. Zota AR, Geller RJ, Calafat AM, Marfori CQ, Baccarelli AA, Moawad GN. Phthalates exposure and uterine fibroid burden among women undergoing surgical treatment for fibroids: a preliminary study. Fertil Steril 2019;111:112–21.
22. Wang Y, Qian H. Phthalates and their impacts on human health. Healthcare (Basel) 2021;9:603.
23. Zota AR, Shamasunder B. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. Am J Obstet Gynecol 2017;217:418.e1–6.
24. Cottrell BH. Vaginal douching. J Obstet Gynecol Neonatal Nurs 2003;32:12–8.
25. Aral SO, Mosher WD, Cates W Jr. Vaginal douching among women of reproductive age in the united states: 1988. Am J Public Health 1992;82:210–4.
26. Oh MK, Merchant JS, Brown P. Douching behavior in high-risk adolescents. What do they use, when and why do they douche? J Pediatr Adolesc Gynecol 2002;15:83–8.
27. Velez Edwards DR, Baird DD, Hartmann KE. Association of age at menarche with increasing number of fibroids in a cohort of women who underwent standardized ultrasound assessment. Am J Epidemiol 2013;178:426–33.
28. Chumlea WC, Schubert CM, Roche AF, et al. Age at menarche and racial comparisons in us girls. Pediatrics 2003;111:110–3.
29. Sandler DP, Hodgson ME, Deming-Halverson SL, et al. The sister study cohort: baseline methods and participant characteristics. Environ Health Perspect 2017;125:127003.
30. O'Brien KM, Ogunsina K, Wentzensen N, Sandler DP. Douching and genital talc use: patterns of use and reliability of self-reported exposure. Epidemiology 2023;34:376–84.
31. Yuan Y. Multiple imputation using SAS software. J Stat Softw 2011;45:1–25.
32. Assmann SF, Hosmer DW, Lemeshow S, Mundt KA. Confidence intervals for measures of interaction. Epidemiology 1996;7:286–90.
33. Zou GY. On the estimation of additive interaction by use of the four-by-two table and beyond. Am J Epidemiol 2008;168:212–24.
34. D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP. Early-life exposures and early-onset uterine leiomyomata in black women in the sister study. Environ Health Perspect 2012;120:406–12.
35. Merchant JS, Oh K, Klerman LV. Douching: a problem for adolescent girls and young women. Arch Pediatr Adolesc Med 1999;153:834–7.
36. Lewis FMT, Diesel J. Intravaginal practices among women attending a sexually transmitted disease clinic-Philadelphia, 2017. Sex Transm Dis 2021;48:e64–7.
37. Fernandez H. [Uterine fibroids]. Rev Prat 2014;64:540–4.
38. Schildkraut JM, Abbott SE, Alberg AJ, et al. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). Cancer Epidemiol Biomarkers Prev 2016;25:1411–7.
39. Faerstein E, Szklo M, Rosenshein NB. Risk factors for uterine leiomyoma: a practice-based case-control study. II. Atherogenic risk factors and potential sources of uterine irritation. Am J Epidemiol 2001;153:11–9.
40. Tran TH, Steffen JE, Clancy KM, Bird T, Egilman DS. Talc, asbestos, and epidemiology: corporate influence and scientific incognizance. Epidemiology 2019;30:783–8.
41. Nikitakis J, McEwen G Jr. CTFA compendium of cosmetic ingredient composition-specifications. Washington, DC: Certified Trust and Fiduciary Advisor; 1990.
42. Ghosh A, Tripathy A, Ghosh D. Impact of endocrine disrupting chemicals (EDCs) on reproductive health of human. Proc Zool Soc 2022;75:16–30.
43. Cramer DW, Vitonis AF, Terry KL, Welch WR, Titus LJ. The association between talc use and ovarian cancer: a retrospective case-control study in two US states. Epidemiology 2016;27:334–46.

44. McDonald SA, Fan Y, Welch WR, Cramer DW, Godleski JJ. Migration of talc from the perineum to multiple pelvic organ sites. Am J Clin Pathol 2019;152:590–607.
45. Buz'Zard AR, Lau BH. Pycnogenol reduces talc-induced neoplastic transformation in human ovarian cell cultures. Phytother Res 2007;21:579–86.
46. Diplock AT, Charleux JL, Crozier-Willi G, et al. Functional food science and defence against reactive oxidative species. Br J Nutr 1998;80(Suppl1):S77–112.
47. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. Int J Biochem Cell Biol 2007;39:44–84.
48. Li Y, Xu X, Asif H, et al. Myometrial oxidative stress drives med12 mutations in leiomyoma. Cell Biosci 2022;12:111.
49. Medikare V, Kandukuri LR, Ananthapur V, Deenadayal M, Nallari P. The genetic bases of uterine fibroids; a review. J Reprod Infertil 2011;12:181–91.
50. Wood CL, Lane LC, Cheetham T. Puberty: normal physiology (brief overview). Best Pract Res Clin Endocrinol Metab 2019;33:101265.
51. Lee PA, Xenakis T, Winer J, Matsenbaugh S. Puberty in girls: correlation of serum levels of gonadotropins, prolactin, androgens, estrogens, and progestins with physical changes. J Clin Endocrinol Metab 1976;43:775–84.
52. Wegienka G. Are uterine leiomyoma a consequence of a chronically inflammatory immune system? Med Hypotheses 2012;79:226–31.
53. Orciani M, Caffarini M, Biagini A, et al. Chronic inflammation may enhance leiomyoma development by the involvement of progenitor cells. Stem Cells Int 2018;2018:1716246.
54. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, prevalence, and treatment of uterine fibroids: a survey of U.S. women. J Womens Health (Larchmt) 2018;27:1359–67.

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